REMARKS/ARGUMENTS

Status of the Claims

Upon entry of the present amendment, claims 4-8 and 15-23 are pending. Claims 4-6 are amended. New claims 15-23 are added.

Claims 4-6 are amended to set forth specific concentrations of HGF and FGF-2. Support is found, for example, on page 16, line 24 through page 17, line 1.

New claims 15 and 16 find support, for example, on page 16, line 24 through page 17, line 1.

New claim 17 finds support, for example, on page 29, lines 15-16.

New claim 18 finds support, for example, on page 37, line 16 through page 38, line 6.

New claims 19-21 find support, for example, on page 29, lines 3-22 and throughout the specification. It is clear that the culturing conditions of the present invention were carried out under atmospheric oxygen levels.

New claim 22, finds support, for example, on page 8, lines 17-20.

New claim 23 finds support, for example, on page 8, lines 21-22.

The present amendments are necessary to place the claims in form for allowance or to reduce issues for appeal. No new matter is added by the present amendments, and the Examiner is respectfully requested to enter them.

Claim Objections

The Examiner objected to claims 4-6 for reciting non-elected subject matter. This objection is obviated by amendment of claims 4-6 to cancel recitation of non-elected subject matter.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 6-8 under 35 U.S.C. § 112, second paragraph, as allegedly unclear. Applicants do not agree with the Examiner. However, in the interest of

furthering prosecution, Applicants have amended claim 6 to set forth the step of culturing cells under conditions that allow their differentiation into a population of cells containing neurons and glia.

Rejection under 35 U.S.C. § 102(e)

The Examiner has maintained the rejection of claims 4-6 and 8 under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 6,589,728 ("Csete"). Applicants do not agree with the Examiner. However, in the interest of furthering prosecution, Applicants have amended claims 4-6 to set forth particular concentrations of HGF and FGF-2. Csete does not teach or suggest particularly using HGF and FGF-2 to culture, proliferate or differentiate neural stem cells, much less teach or suggest a particular concentration range for either growth factor. Furthermore, the invention in Csete relies on subatmospheric oxygen levels in culture (*i.e.*, less than 12% in the claims). This is reflected in the abstract and claims of Csete.

The Examiner is respectfully reminded that the present invention is a selection invention particularly directed to the culture, proliferation and differentiation of ***neural*** stem cells. The passages in columns 7 and 15 of Csete identified by the Examiner are not entirely consistent with each other. The passage at column 7, lines 42-62 is concerned with ***stem cells generally*** and not neural stem cells in particular. The passage at column 7 does not teach or suggest particularly combining HGF with FGF-2 (*a.k.a.*, bFGF) to culture, proliferate or differentiate any kind of stem cell, much less particularly neural stem cells.

The passage at column 15, lines 51-65 of Csete is expressly directed to isolating and culturing neural stem cells. Csete discloses that neuroepithelial stem cells can be cultured and proliferated in FGF-2 (bFGF), but does not disclose or suggest combining FGF-2 with HGF. With respect to differentiation of neural stem cells into neurons and glia, Csete affirmatively states that the FGF-2 (bFGF) is removed and replaced with media lacking FGF-2. Therefore, in the passage at column 15, lines 63-65, Csete expressly teaches that differentiation of neural stem cells is performed in the absence of FGF-2 and does not teach or suggest adding HGF for the purpose of culturing, proliferating or differentiating neural stem cells. The Examiner can not

give greater weight to the general disclosure of Csete in column 7 while ignoring the disclosure particular to neural stem cells at column 15.

Because Csete does not teach or suggest each and every element of the claimed methods, Csete does not anticipate the present invention. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

Rejection under 35 U.S.C. § 103(a)

The Examiner has rejected claim 7 under 35 U.S.C. § 103(a) as allegedly obvious over Csete in view of U.S. Patent No. 5,753,505 ("Luskin"). To the extent that the present rejection applies to the present claims, Applicants respectfully traverse.

Applicants maintain the position that the combined disclosures of Csete and Luskin do not teach or suggest all of the steps and elements of the claimed methods. The Examiner is respectfully reminded that the present methods are a selection invention particularly directed to the culture, proliferation and differentiation of ***neural stem cells*** by culturing them in a growth medium comprising the particularly selected ***combination of HGF and FGF-2***. As discussed previously, in the passage in column 7 of Csete, no particular combination of growth factors is called out and no particular stem cell type is called out. As a matter of enablement of Csete as a reference, the skilled person is still left to determine which out of the myriad of permutations of growth factors and stem cell types to match up for the culture, proliferation and/or differentiation conditions particular to neural stem cells. Where Csete does expressly discuss neural stem cells in the passage in column 15, Csete ***teaches away*** from the present methods by teaching that FGF-2 is removed prior to differentiation neural stem cells. Csete makes absolutely *no mention of HGF in the growth medium of neural stem cells.*

With respect to the amended claims, Csete does not teach or suggest the particular concentrations of growth factors. Csete certainly teaches against the use of atmospheric concentrations of oxygen in culturing, proliferating, or differentiating any kind of stem cell, including neural stem cells. *See, e.g.*, abstract, summary and claims of Csete. As stated previously, Luskin does not cure the deficiencies of Csete. Luskin discloses adding ***nerve***

growth factor (NGF) or brain-derived neurotrophic factor (BDNF) to the growth medium of neural stem cells, but does not teach or suggest in any way that ***hepatocyte growth factor*** would find use in culturing, proliferating or differentiation ***neural stem cells***. Based on the disclosures of Csete and Luskin, the skilled person would have no reason to expect that a liver cell growth factor should promote differentiation of nerve stem cells, for example, into neurons.

In any case, Applicants have rebutted any alleged *prima facie* case of obviousness by demonstrating an unexpected synergistic effect of HGF and FGF-2 in promoting the growth and differentiation of neural stem cells. This is shown in columns 1-3 of Table 1 on page 35 of the present application. The Examiner alleges that the synergistic effects of HGF and FGF2 are not unexpected because HGF and FGF-2 are structurally and functionally distinct growth factors. *See*, pages 4-5 of the present Office Action. However, FGF-2 and EGF also are structurally and functionally distinct growth factors,[1] and their combined effects were less than additive. *See*, columns 2 (FGF-2 only), 4 (EGF only) and 6 (FGF-2 and EGF) of Table 1. There is no *a priori* reason for the skilled person to expect that the combination of HGF and FGF-2 should be synergistic and the combination of FGF-2 and EGF be less than additive in promoting the proliferation of neural stem cells.

Also, the differentiated neural cell populations are different in the presence or absence of HGF. In the presence of HGF, a majority of the differentiated cells are neurons. In the presence of EGF and FGF-2, but in the absence of HGF, only about 30% of the differentiated cells are neurons. *See*, *e.g.*, page 37, lines 16-24 of the present application.

In view of the foregoing, the combined disclosures of Csete and Luskin do not render the present methods obvious. Accordingly, the Examiner is respectfully requested to withdraw the present rejection.

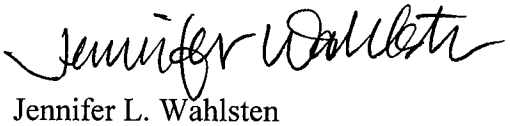
[1] Amino acid sequences and BLAST alignments of human HGF, FGF-2 and EGF are attached as Exhibit A.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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Attachments
JLW:jlw
61201308 v1

1: NP_001954. Reports epidermal growth ...[gi:4503491]

BLink, Conserved Domains, Links

Comment Features Sequence

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VERSION     NP_001954.1  GI:4503491
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REFERENCE   1  (residues 1 to 1207)
  AUTHORS   Toyoda,T., Nakamura,K., Yamada,K., Thanseem,I., Anitha,A., Suda,S.,
            Tsujii,M., Iwayama,Y., Hattori,E., Toyota,T., Miyachi,T., Iwata,Y.,
            Suzuki,K., Matsuzaki,H., Kawai,M., Sekine,Y., Tsuchiya,K.,
            Sugihara,G., Ouchi,Y., Sugiyama,T., Takei,N., Yoshikawa,T. and
            Mori,N.
  TITLE     SNP analyses of growth factor genes EGF, TGFbeta-1, and HGF reveal
            haplotypic association of EGF with autism
  JOURNAL   Biochem. Biophys. Res. Commun. 360 (4), 715-720 (2007)
   PUBMED   17626784
  REMARK    GeneRIF: suggest a possible role of EGF in the pathogenesis of
            autism
REFERENCE   2  (residues 1 to 1207)
  AUTHORS   Diehl,K.M., Grewal,N., Ethier,S.P. and Woods-Ignatoski,K.M.
  TITLE     p38MAPK-activated AKT in HER-2 overexpressing human breast cancer
            cells acts as an EGF-independent survival signal
  JOURNAL   J. Surg. Res. 142 (1), 162-169 (2007)
   PUBMED   17612563
  REMARK    GeneRIF: In the absence of EGF, p38MAPK-activated AKT is necessary
            for HER-2 overexpressing human breast cancer cells to survive and
            to form colonies in soft agar.
REFERENCE   3  (residues 1 to 1207)
  AUTHORS   Meisdalen,K., Dajani,O.F., Christoffersen,T. and Sandnes,D.
  TITLE     Prostaglandins enhance epidermal growth factor-induced DNA
            synthesis in hepatocytes by stimulation of E prostanoid 3 and F
            prostanoid receptors
  JOURNAL   J. Pharmacol. Exp. Ther. 322 (3), 1044-1050 (2007)
   PUBMED   17567965
  REMARK    GeneRIF: role of E prostanoid receptors EP1, EP2, & EP3 and F
            prostanoid receptors in enhancing the growth-stimulatory effect of
            epidermal growth factor in cultured hepatocytes
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Exhibit A

REFERENCE 4 (residues 1 to 1207)
AUTHORS Su,X., Kong,C. and Stahl,P.D.
TITLE GAPex-5 mediates ubiquitination, trafficking, and degradation of epidermal growth factor receptor
JOURNAL J. Biol. Chem. 282 (29), 21278-21284 (2007)
PUBMED 17545148
REMARK GeneRIF: EGF-stimulated receptor ubiquitination and trafficking are mediated via GAPex-5: GAPex-5-mediated EGFR ubiquitination is independent of Rab5 activation
REFERENCE 5 (residues 1 to 1207)
AUTHORS Durer,U., Hartig,R., Bang,S., Thim,L. and Hoffmann,W.
TITLE TFF3 and EGF induce different migration patterns of intestinal epithelial cells in vitro and trigger increased internalization of E-cadherin
JOURNAL Cell. Physiol. Biochem. 20 (5), 329-346 (2007)
PUBMED 17762162
REMARK GeneRIF: trefoil factor 3, in contrast to EGF, enhanced a collective cell migration ensuring a precise coverage of the re-populated area avoiding gaps
REFERENCE 6 (sites)
AUTHORS Skidgel,R.A., McGwire,G.B. and Li,X.Y.
TITLE Membrane anchoring and release of carboxypeptidase M: implications for extracellular hydrolysis of peptide hormones
JOURNAL Immunopharmacology 32 (1-3), 48-52 (1996)
PUBMED 8796265
REFERENCE 7 (sites)
AUTHORS McGwire,G.B. and Skidgel,R.A.
TITLE Extracellular conversion of epidermal growth factor (EGF) to des-Arg53-EGF by carboxypeptidase M
JOURNAL J. Biol. Chem. 270 (29), 17154-17158 (1995)
PUBMED 7615511
REFERENCE 8 (residues 1 to 1207)
AUTHORS Ishibashi,T., Bottaro,D.P., Chan,A., Miki,T. and Aaronson,S.A.
TITLE Expression cloning of a human dual-specificity phosphatase
JOURNAL Proc. Natl. Acad. Sci. U.S.A. 89 (24), 12170-12174 (1992)
PUBMED 1281549
REFERENCE 9 (residues 1 to 1207)
AUTHORS Gout,I., Dhand,R., Panayotou,G., Fry,M.J., Hiles,I., Otsu,M. and Waterfield,M.D.
TITLE Expression and characterization of the p85 subunit of the phosphatidylinositol 3-kinase complex and a related p85 beta protein by using the baculovirus expression system
JOURNAL Biochem. J. 288 (PT 2), 395-405 (1992)
PUBMED 1334406
REFERENCE 10 (residues 1 to 1207)
AUTHORS Hommel,U., Harvey,T.S., Driscoll,P.C. and Campbell,I.D.
TITLE Human epidermal growth factor. High resolution solution structure and comparison with human transforming growth factor alpha
JOURNAL J. Mol. Biol. 227 (1), 271-282 (1992)
PUBMED 1522591
REFERENCE 11 (residues 1 to 1207)
AUTHORS Lei,Z.M. and Rao,C.V.
TITLE Expression of epidermal growth factor (EGF) receptor and its ligands, EGF and transforming growth factor-alpha, in human fallopian tubes
JOURNAL Endocrinology 131 (2), 947-957 (1992)
PUBMED 1639032
REFERENCE 12 (residues 1 to 1207)
AUTHORS Gregory,H. and Preston,B.M.
TITLE The primary structure of human urogastrone

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            Publication Note:  This RefSeq record includes a subset of the
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            Entrez Gene record to access additional publications.
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Aug 28 2007 16:53:42

☐ 1: AAA64297. Reports hepatocyte growth...[gi:337938]

BLink, Conserved Domains, Links

Features Sequence

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REFERENCE   1  (residues 1 to 723)
  AUTHORS   Weidner,K.M., Arakaki,N., Hartmann,G., Vandekerckhove,J.S.,
            Weingart,S., Rieder,H., Fonatsch,C., Tsubouchi,H., Hishida,T.,
            Daikuhara,Y. and Birchmeier,W.
  TITLE     Evidence for the identity of human scatter factor and human
            hepatocyte growth factor
  JOURNAL   Proc. Natl. Acad. Sci. U.S.A. 88 (16), 7001-7005 (1991)
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☐ **1:** NP_001997. Reports fibroblast growth...[gi:153285461]

BLink, Conserved Domains, Links

Comment Features Sequence

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DEFINITION  fibroblast growth factor 2 [Homo sapiens].
ACCESSION   NP_001997
VERSION     NP_001997.5  GI:153285461
DBSOURCE    REFSEQ: accession NM_002006.4
KEYWORDS    .
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
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            Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini;
            Catarrhini; Hominidae; Homo.
REFERENCE   1  (residues 1 to 288)
  AUTHORS   Shi,Y.H., Bingle,L., Gong,L.H., Wang,Y.X., Corke,K.P. and Fang,W.G.
  TITLE     Basic FGF augments hypoxia induced HIF-1-alpha expression and VEGF
            release in T47D breast cancer cells
  JOURNAL   Pathology 39 (4), 396-400 (2007)
   PUBMED   17676480
  REMARK    GeneRIF: bFGF augments hypoxia induced VEGF release in breast
            cancer cells mainly through the PI3K pathway and partly depending
            on HIF-1 activity.
REFERENCE   2  (residues 1 to 288)
  AUTHORS   D'Sa,C., Gross,J., Francone,V.P. and Morest,D.K.
  TITLE     Plasticity of synaptic endings in the cochlear nucleus following
            noise-induced hearing loss is facilitated in the adult FGF2
            overexpressor mouse
  JOURNAL   Eur. J. Neurosci. 26 (3), 666-680 (2007)
   PUBMED   17651425
  REMARK    GeneRIF: FGF2 may contribute to the synaptic reorganization after
            noise damage; it may protect and/or aid recovery of synapses after
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REFERENCE   3  (residues 1 to 288)
  AUTHORS   Kakudo,N., Shimotsuma,A. and Kusumoto,K.
  TITLE     Fibroblast growth factor-2 stimulates adipogenic differentiation of
            human adipose-derived stem cells
  JOURNAL   Biochem. Biophys. Res. Commun. 359 (2), 239-244 (2007)
   PUBMED   17543283
  REMARK    GeneRIF: Fibroblast growth factor-2 stimulates adipogenic
            differentiation of human adipose-derived stem cells
REFERENCE   4  (residues 1 to 288)
  AUTHORS   Ribatti,D., Vacca,A., Rusnati,M. and Presta,M.
  TITLE     The discovery of basic fibroblast growth factor/fibroblast growth
            factor-2 and its role in haematological malignancies
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JOURNAL Cytokine Growth Factor Rev. 18 (3-4), 327-334 (2007)
PUBMED 17537668
REMARK GeneRIF: FGF2 has a role in tumor angiogenesis associated with haematological malignancies [review]
Review article
REFERENCE 5 (residues 1 to 288)
AUTHORS Arnaud,E., Touriol,C., Boutonnet,C., Gensac,M.C., Vagner,S., Prats,H. and Prats,A.C.
TITLE A new 34-kilodalton isoform of human fibroblast growth factor 2 is cap dependently synthesized by using a non-AUG start codon and behaves as a survival factor
JOURNAL Mol. Cell. Biol. 19 (1), 505-514 (1999)
PUBMED 9858574
REMARK GeneRIF: A new FGF2 isoform results from the use of a non-AUG (CUG) translation initiation codon.
REFERENCE 6 (residues 1 to 288)
AUTHORS Watson,R., Anthony,F., Pickett,M., Lambden,P., Masson,G.M. and Thomas,E.J.
TITLE Reverse transcription with nested polymerase chain reaction shows expression of basic fibroblast growth factor transcripts in human granulosa and cumulus cells from in vitro fertilisation patients
JOURNAL Biochem. Biophys. Res. Commun. 187 (3), 1227-1231 (1992)
PUBMED 1417798
REFERENCE 7 (residues 1 to 288)
AUTHORS Ago,H., Kitagawa,Y., Fujishima,A., Matsuura,Y. and Katsube,Y.
TITLE Crystal structure of basic fibroblast growth factor at 1.6 A resolution
JOURNAL J. Biochem. 110 (3), 360-363 (1991)
PUBMED 1769963
REFERENCE 8 (residues 1 to 288)
AUTHORS Eriksson,A.E., Cousens,L.S., Weaver,L.H. and Matthews,B.W.
TITLE Three-dimensional structure of human basic fibroblast growth factor
JOURNAL Proc. Natl. Acad. Sci. U.S.A. 88 (8), 3441-3445 (1991)
PUBMED 1707542
REFERENCE 9 (residues 1 to 288)
AUTHORS Zhu,X., Komiya,H., Chirino,A., Faham,S., Fox,G.M., Arakawa,T., Hsu,B.T. and Rees,D.C.
TITLE Three-dimensional structures of acidic and basic fibroblast growth factors
JOURNAL Science 251 (4989), 90-93 (1991)
PUBMED 1702556
REFERENCE 10 (residues 1 to 288)
AUTHORS Prats,H., Kaghad,M., Prats,A.C., Klagsbrun,M., Lelias,J.M., Liauzun,P., Chalon,P., Tauber,J.P., Amalric,F., Smith,J.A. et al.
TITLE High molecular mass forms of basic fibroblast growth factor are initiated by alternative CUG codons
JOURNAL Proc. Natl. Acad. Sci. U.S.A. 86 (6), 1836-1840 (1989)
PUBMED 2538817
REMARK GeneRIF: Alternate protein isoforms arise through the use of AUG and non-AUG (CUG) translation initiation codons.
COMMENT REVIEWED REFSEQ: This record has been curated by NCBI staff. The reference sequence was derived from J04513.1, AC021205.6, M27968.1, BU501243.1, BP292299.1, CN315083.1 and AA256481.1.
On Jul 24, 2007 this sequence version replaced gi:41352695.

Summary: The protein encoded by this gene is a member of the fibroblast growth factor (FGF) family. FGF family members bind heparin and possess broad mitogenic and angiogenic activities. This protein has been implicated in diverse biological processes, such as limb and nervous system development, wound healing, and tumor

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            growth. The mRNA for this gene contains multiple polyadenylation
            sites, and is alternatively translated from non-AUG (CUG) and AUG
            initiation codons, resulting in five different isoforms with
            distinct properties. The CUG-initiated isoforms are localized in
            the nucleus and are responsible for the intracrine effect, whereas,
            the AUG-initiated form is mostly cytosolic and is responsible for
            the paracrine and autocrine effects of this FGF.

            Publication Note:  This RefSeq record includes a subset of the
            publications that are available for this gene. Please see the
            Entrez Gene record to access additional publications.
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Blast 2 Sequences results

PubMed Entrez BLAST OMIM Taxonomy Structure

BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.17 [Aug-26-2007]

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x_dropoff: 0 expect: 10.000(wordsize: 3 Filter ☐ View option Standard
Masking character option X for protein, n for nucleotide Masking color option Black
☐ Show CDS translation Align

Sequence 1: unnamed protein product EGF
Length = 1207

Sequence 2: unnamed protein product HGF
Length = 723

No significant similarity was found

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CPU time:     0.03 user secs.       0.02 sys. secs          0.05 total secs.
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Blast 2 Sequences results

PubMed Entrez BLAST OMIM Taxonomy Structure

BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.17 [Aug-26-2007]

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x_dropoff: 0 expect: 10.000(wordsize: 3 Filter ☐ View option Standard
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☐ Show CDS translation Align

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Sequence 2: unnamed protein product FGF-2
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No significant similarity was found

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Blast 2 Sequences results

PubMed Entrez BLAST OMIM Taxonomy Structure

BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.17 [Aug-26-2007]

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x_dropoff: 0 expect: 10.000(wordsize: 3 Filter ☐ View option Standard
Masking character option X for protein, n for nucleotide Masking color option Black
☐ Show CDS translation Align

Sequence 1: unnamed protein product HGF
Length = 723

Sequence 2: unnamed protein product FGF-2
Length = 288

No significant similarity was found

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CPU time:     0.03 user secs.       0.02 sys. secs          0.05 total secs.
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